## REMARKS

Claims 1-39 are cancelled, with claims 22-31 being cancelled previously, and new claims 40-64 are added to replace the cancelled claims. New claims 40-64 are supported by the original claims and specification. For example, the specification at the following pages provides support for the new claims: page 2, lines 2-5, page 5, lines 11-26 and Example 1 (claim 40); page 9, line 30 to page 10, line 2 and Example 1 (claim 41); page 9, lines 11-16 and page 10, lines 3-4 (claims 42 and 46); page 8, lines 19-32 (claim 43); page 5, lines 9-20 (claims 44-45); page 3, line 12 to page 4, line 2 (claims 47-48 and 60-61); page 4, lines 3-30 (claims 49 and 62); page 4, line 31 to page 5, line 8 (claim 50); page 5, lines 27-31 (claim 51); page 6, lines 10-18 (claims 52-53 and 63-64); page 7, lines 1-15 (claims 54-55); page 7, lines 16-23 and Example 2 (claims 56); page 7, lines 1-31 (claims 57-58); and Example 5 (claims 59-64).

The title is also amended to better reflect the new claims. As no new matter is added, Applicants respectfully request that the amended claims and title be entered at this time.

The cancellation of claims 1-21 and 32-39 renders the rejections stated in the Office Action moot. Accordingly, all the rejections should be withdrawn.

Upon filing of the Request for Continued Examination, Applicants submit new claims relating to a method for increasing bioavailability of a lipophilic bioactive compound (LBC) when administered to a subject and to a method of providing increased photostability and oxidation resistance to a lipophilic bioactive compound by associating the lipophilic compound with a whey protein.

As noted in the specification, the present invention relates to increasing the bioavailability of a lipophilic bioactive compound by the novel feature of associating the lipophilic bioactive compound with a whey protein to form a mixture (*see, e.g.*, specification, p. 5, lines 21-24; p. 7, lines 1-4; p. 8, lines 12-18; p. 8, line 19 to p. 10, line 11). A primary composition in the form of dispersion, gel or powder may be prepared from an LBC-whey protein mixture according to the present claims (p. 8, line 19 to p. 10, line 11), and the LBC may be obtained, extracted, enriched or purified from a plant, microorganism, yeast or product of animal origin (p. 3, line 12 to p. 4, line 2). Bioavailability of a lipophilic bioactive compound may be increased by administering a foodstuff, a food supplement or a pharmaceutical preparation to which such primary composition has been added (p. 6, line 32 to p. 7, line 31). By mixing an LBC with a whey protein, the present invention makes

available to a subject an LBC-containing composition with better bioavailability compared to consuming an LBC alone (p. 3, lines 6-8; p. 5, lines 11-14).

Further, as summarized in Example 1, administration of Applicants' composition -- formed by associating a lipophilic bioactive compound, such as lycopene, with a whey protein -- has shown that the composition's LBC bioavailability is comparable to that of tomato puree or paste, which is known to have the best bioavailability of lycopene. The data from the study outlined in Example 1 is submitted herewith as Exhibit A.

Applicants surprisingly discovered that, by mixing an LBC with whey protein in the same composition, the level of bioavailability of the LBC is unexpectedly and significantly enhanced. Although the prior art has recognized the beneficial effects of an LBC, it has not been known that whey protein possesses the particular LBC-protective and bioavailability-enhancing functions which can be advantageously utilized by mixing a whey protein and an LBC to form a homogeneous composition.

The prior art references previously cited by the Examiner in the Office Action have sought to provide bioactive compounds for health-related purposes (*see, e.g.*, Potter *et al.* (U.S. Patent No. 5,855,892) (providing daidzein that is preferably isolated from soy material such as soy whey protein and daidzein-rich soy protein material); Fujiwara *et al.* (U.S. Patent No. 5,705,526) (providing a soft-capsulated drug with lycopene in mixture with wheat germ oil and vegetable oil, which are present to improve the fluidity of the contents of the capsule); Collins *et al.* (U.S. Patent No. 6,203, 805) (providing a composition containing whey protein and vitamins A, C, and E, wherein vitamins E and C are present in certain absolute and relative quantities to enhance collagen synthesis)); Schmitz *et al.* (U.S. Patent No. 5,643,623) (providing a food product in which a first component of antioxidant is embedded within or discrete from a second component of fat, carbohydrate or protein). None of these references, however, has recognized the bioavailability-enhancing functions of whey protein that can be utilized by mixing the whey protein with an LBC or taught the presently claimed methods.

Further, although Rosenberg *et al.* (U.S. Patent No. 5,601,760) discloses whey protein-based microencapsulating agents that can be used with volatile or non-volatile core materials, whey protein in Rosenberg is provided merely as a carrier for encapsulating and delivering the core material. Because Rosenberg seeks to utilize the suitability of whey protein as a microencapsulating agent based on its stability, safety for consumption, and ease of handling and storage, Rosenberg uses whey protein in a manner that is completely different from that of the present claims. Specifically, rather than being mixed with an LBC

in a mixture, the whey protein in Rosenberg encapsulates a core material, completely coating the core material such that it is shielded from light, air and physical contact. In contrast to the prior art, the whey protein according to the present claims does not cover or embed an LBC but is mixed with it such that the bioavailability of the LBC is enhanced.

New claims 59-64 are directed to a method of providing increased photostability and oxidation resistance to a lipophilic bioactive compound. As explained in Example 5 (p. 12) of the present specification, associating a lipophilic bioactive compound with a whey protein results in increased resistance of the lipophilic bioactive compound to decomposition by light and oxygen because of the unexpected protective function of the whey protein. Unlike the prior art, in which the stability of a core material is increased by physically covering it with protein or whey protein and shielding it from light and air (*see* Schmitz; Rosenberg), the present method seeks to increase an LBC's resistance to degradation caused by light and air by associating the LBC with whey protein in a mixture. Even though the LBC according to the present method is exposed to light and air, its stability is greatly enhanced when mixed with whey protein as shown in Example 5 (only 10% decomposed after one day when mixed with whey protein versus 60% when the LBC is not mixed with whey protein; only 40% decomposed after two days when mixed with whey protein versus almost all decomposed when not mixed with whey protein).

In view of the claim amendments, it is believed that the entire application is now in condition for allowance, early notification of which would be appreciated. Should the Examiner not agree with this position, a telephone or personal interview is requested to resolve any remaining issues and expedite allowance of this application.

Respectfully submitted,

Date: 7/8/04

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**EXHIBIT A – Study of administration of lycopene-whey protein composition**

See attached sheet titled "A food-based formulation provides lycopene with the same bioavailability to humans as that from tomato paste," published May 30, 2001. The publication analyzes the data from a study involving administration of a composition formed by associating lycopene and whey proteins.

# A food-based formulation provides lycopene with the same bioavailability to humans as that from tomato paste

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## Background

Lycopene from fresh tomatoes or tomato extracts is poorly absorbed in man. Processing of tomatoes increases absorption of lycopene: tomato paste > tomato juice heated in oil.

## Aim

To develop a food-grade lycopene formulation, which is bioavailable in man.

## Experimental design

A food-based formulation of lycopene has been designed consisting of entrapment of lycopene (Lycomato ™ 6%) with whey proteins.

Thirty six healthy subjects were recruited for this study. They were asked to refrain for dietary lycopene intake for the entire study, i.e. 11 weeks. After a three week deprivation period of dietary lycopene intake, subjects ingested daily 25 mg lycopene over 8 weeks period. Twelve subjects were allocated to one of the following three groups:

a) lycopene formulation (lactolycopene);
b) tomato paste (positive control);
c) a placebo of whey proteins

Composition of the lycopene supplements

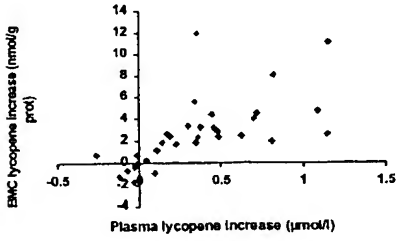
| | Lycopene formulation | Tomato paste |
|---|---|---|
| α-tocopherol | 0.014 | 0.098 |
| β -tocopherol | 0.099 | 0.483 |
| γ -tocopherol | 0.025 | 0.131 |
| Lycopene | 0.751 | 1.972 |
| Phytofluene | 0.06 | 0.13 |
| Phytoene | 0.11 | 0.25 |

Composition expressed in mg/g product

*Determination of lycopene*: Plasma and buccal mucosa samples were extracted. Lycopene were isolated from other carotenoids and tocopherols by HPLC using a C18 RP column and further quantified by UV/Vis detector.

*Determination of lycopene isomers*: The lycopene peak from the above HPLC run was collected and further submitted to a second HPLC separation using Nucleosil 300-5 columns. Different cis isomers of lycopene were isolated from the all-trans isomer.

### Correlation plasma lycopene vs buccal mucosa cell lycopene



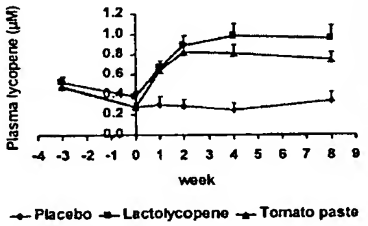

## Conclusions

1. The food-based formulation and tomato paste exhibited similar lycopene bioavailability in plasma and buccal mucosa cells in humans.
2. Lycopene underwent isomerization in vivo.

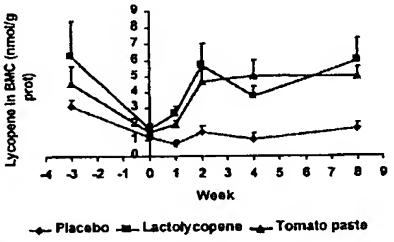
## Results

1. Plasma lycopene concentrations reached a maximum after two weeks of supplementation and then plateaued until the end of the treatment.
2. Mean (±SEM) increases in plasma lycopene at week 8 were similar with lycopene formulation and with tomato paste.
3. Pharmacokinetic of buccal mucosa cell lycopene paralleled that of plasma lycopene.
4. Although lycopene was mainly present as all-*trans* isomers (>90 %) in both lycopene supplements, plasma lycopene enrichment consisted of 40% as all-*trans* and 60% as *cis* isomers.
5. The precursor of lycopene, phytofluene, was better absorbed than lycopene itself.

### Plasma lycopene




### Buccal mucosa cell lycopene




### Lycopene isomer profile in supplements and in plasma

| % | Lactolycopene Supplement | Lactolycopene Plasma week 0 | Lactolycopene Plasma week 8 | Tomato paste Supplement | Tomato paste Plasma week 0 | Tomato paste Plasma week 8 |
|---|---|---|---|---|---|---|
| all-trans | 92 | 38±3 | 36±1 | 95 | 33±1 | 39±1 |
| 5-cis | 8 | 28±1 | 26±1 | 5 | 28±1 | 22±1 |
| 9-cis | | 5±0 | 7±0 | | 5±0 | 4±0 |
| 13-cis | | 11±1 | 12±0 | | 14±1 | 15±1 |
| 15-cis | | 5±1 | 5±0 | | 7±1 | 6±0 |
| Unidentified cis isomers | | 13±1 | 14±1 | | 13±1 | 15±1 |

### Phytofluene and lycopene concentration in supplements and in plasma

| | Plasma phytofluene Supplement mg | Week 0 µM | Week 8 µM | Change µM | Plasma lycopene Supplement mg | Week 0 µM | Week 8 µM | Change µM |
|---|---|---|---|---|---|---|---|---|
| Placebo | 0 | 0.2±0 | 0.2±0 | 0±0 | 0 | 0.3±0 | 0.3±0.1 | 0.1±0.1 |
| Lactolycopene | 2 | 0.2±0 | 0.4±0.1 | 0.2±0.1 | 25 | 0.4±0.1 | 1.0±0.1 | 0.6±0.1 |
| Tomato paste | 2 | 0.2±0.2 | 0.5±0.1 | 0.3±0.1 | 25 | 0.3±0 | 0.8±0.1 | 0.5±0.1 |